

# Innovation in Development, Regulatory Review, and Use of Clinical Advances

## A Vital Direction for Health and Health Care

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### Introduction

This paper describes issues and challenges in inventing and regulating new medicines, vaccines, and devices and in integrating these advances into clinical practices as rapidly as appropriate and possible. It describes the landscape of discovery and invention, evaluation of efficacy and safety, determination of value, and postapproval surveillance and identifies windows of opportunity. It provides the rationale for markedly enhanced patient input throughout the process from target identification to decisions regarding insurance coverage. It describes the role of academe–industry collaboration in speeding the translation of research

findings into health benefits and emphasizes the opportunity for medical education at multiple levels to realize the value of therapeutic innovations to society. Finally, it offers high-priority recommendations.

### Context and Types of Opportunities

The pharmaceutical and biotechnology sectors experienced considerable challenges during the first decade of the 21st century. Stagnant research and development (R&D) productivity and the slow pace and high cost of drug development led many to argue for new approaches to discovery, manufacturing, development, and commercialization of new products to meet

patients' needs. Estimated costs for bringing a new drug to market through the research, development, and regulatory processes may be as much as \$2.6 billion, a substantial increase over the previous decade (TCSDD, 2015). The complexities of the analytics and cost attributions present challenges that are sources of active discussion, but there is no question that the costs are substantial. Furthermore, about 85% of therapies fail through early clinical development, and only half those surviving to Phase III will be approved (Ledford, 2011). Some have argued that this "clinical-trial cliff" results from losing a substantial number of good drugs to outdated and impractical clinical-trial designs (Ledford, 2011). Those challenges are forcing all sectors (industry, regulators, academe, government agencies, and patient advocacies) to evaluate opportunities to replace traditional drug-development paradigms with newer and more efficient models (Boname et al., 2016; IOM, 2010; Kaitlin and Honig, 2013).

Favorable trends in new-product approvals and breakthrough therapies over the last few years indicate that efforts to adapt to a new landscape of bioinnovation may be starting to pay off. In 2015, the Food and Drug Administration (FDA) approved 45 novel drugs or biologics, more than the average number approved each year during the last decade (28) while applications for new approvals were steady. More "orphan" drugs for rare diseases are being approved than in previous years, and we are seeing regulatory approval of new treatments for broader conditions, such as various forms of cancer, heart failure, hypercholesterolemia, and infectious disease. Furthermore, the use of expedited regulatory pathways (fast track, accelerated approval, priority review, and breakthrough designation) for therapies (60% of novel drugs in 2015) that will offer much to patients in need has accelerated.

In the United States, several initiatives are under way to accelerate pharmaceutical innovation. Eight recommendations in the President's Council of Advisors on Science and Technology 2012 report sought to "double the output of innovative new medicines for patients with important unmet medical needs, while increasing drug efficacy and safety, through industry, academia and government working together to decrease clinical failure, clinical trial costs, time to market and regulatory uncertainty" (PCAST, 2012). The president's ambitious Precision Medicine Initiative ([whitehouse.gov/precision-medicine](http://whitehouse.gov/precision-medicine)) was kicked

off in 2015, and FDA has offered accelerated approval pathways for specialized treatments for rare and life-threatening diseases. Approval of the 21st Century Cures Act by Congress this year could further speed regulatory approvals for therapies that will have a substantial effect on patients' lives. The Critical Path Institute (<https://c-path.org/>) was established in 2005 with the aim of bringing academic, industry, and regulatory scientists together to improve the drug and device development process. TransCelerate BioPharma ([transceleratebiopharmainc.com](http://transceleratebiopharmainc.com)) is a nonprofit organization whose mission is to foster collaboration throughout the biopharmaceutical R&D community to drive more efficient delivery of effective new medicines to improve the health of people worldwide. Finally, the Innovative Medicines Initiative ([imi.europa.eu](http://imi.europa.eu)) is Europe's largest public-private initiative; it was undertaken jointly by the European Union and the pharmaceutical industry to speed the development of better and safer medicines. The number of precompetitive collaborations designed to improve drug development continues to grow, increasing the odds that the future will see improved productivity of innovative therapies.

### Discovery of New Therapies

Opportunities abound to improve efficiency in the discovery phase of new therapy development, including the following:

- *Target "validation."* New targets for drug development are urgently needed, and the Human Genome Project has provided thousands of potential targets. A precompetitive effort to determine which targets are most likely to produce therapeutic value would benefit all stakeholders and increase the success rate of new drug development.
- *Predictive toxicology and efficacy.* Unexpected adverse effects and lack of efficacy despite promising preclinical results in model systems lead to the failure of most potential drugs to progress to approval. New approaches, including pathway-based systems biology and "organ-on-a-chip" systems, have the potential to deliver more efficient and accurate predictions of safety and efficacy and thus to give drug developers real-time human-based information with which to develop new therapies; these new approaches should also provide regulators with a better scientific basis on which to make regulatory decisions.

- *Additional uses for existing drugs.* Potentially the most efficient and safest way to develop a new treatment is to use a drug that is already in development or has been approved for another disease (sometimes referred to as repurposing). Use of mechanism-based nosology would facilitate this approach. The recognition that some diseases traditionally thought to be independent are in fact mechanistically related provides a transformative opportunity to treat several diseases with drugs that have been approved or are in development (particularly compelling examples are immune-oncology therapies). Applying this principle to all diseases and all drugs would require substantial effort.
- *Combination therapies.* Many disorders—such as infectious diseases, cancers, and hypertension—can require more than one drug for adequate treatment. Methods to identify combinations of drug candidates with improved efficacy and reduced safety risk would leverage the many individual therapies already developed and in development. Dedicated technology development, testing, and clinical-development strategies are needed.
- *New gene-based and cell-based therapies.* A recent scientific renaissance of gene therapy, powerful new gene-editing techniques, and the expanding flexibility of stem-cell technologies have the potential to provide transformational therapeutic approaches that are complementary to small-molecule and protein drugs. Most, however, are in the concept stage, and dedicated effort will be required to translate them to application to human disease.
- *Precompetitive collaboration.* Much of the current work in drug discovery and development is in the most challenging therapeutic sectors, such as neurodegenerative, autoimmune, and inflammatory diseases. In addition, endemic outbreaks of antibiotic-resistant bacteria or viral infections—such as Ebola and Zika, many pediatric diseases, and some rare diseases—still lack consistent R&D efforts. Given the lack of complete knowledge of the pathogenesis of such maladies, it is essential that industry, government, and academe appreciate that neither domain is sufficient alone and that they must work together to achieve the needed breakthroughs. The breakthroughs must be approached through more focused and organized precompetitive collaborations involving industry, government,

academia, and other groups. Recent examples of success in the preclinical and clinical spaces include the Accelerating Medicines Partnership ([nih.gov/research-training/accelerating-medicines-partnership-amp](http://nih.gov/research-training/accelerating-medicines-partnership-amp)) in the former and the Alzheimer's Disease Neuroimaging Initiative ([adni-info.org](http://adni-info.org)) in the latter. Such collaborations also hold promise of providing translational-science tools (such as organs-on-a-chip) that permit extrapolation of pre-clinical data to the clinic regarding both efficacy and safety.

### Development of New Therapies

Over two-thirds of the total cost, in both dollars and time, of the discovery and development of a new drug is embedded in the clinical-testing phase. Hence, it is critical that advances in such arenas as biomarkers, patient-reported outcomes, innovative clinical-trial designs, use of real-world evidence (RWE), and precision medicine be deployed in this phase for optimal advantage.

- *Biomarkers.* Biomarkers are biologic indicators that may provide predictive, diagnostic, prognostic, risk, safety, and treatment monitoring information about a patient's condition or disease. Examples are biochemical, genetic, and imaging data that may identify groups of patients who might respond better to a specific intervention or serve as end points in clinical trials that complement or replace clinical end points. However, there is a paucity of qualified or "approved" biomarkers or combinations of biomarkers that can expedite the drug-development and regulatory process. Hence, there is a critical need for a biomarker-qualification process. That requires an understanding of the context of use followed by a consideration of the benefit:risk ratio of the marker and then an understanding of the kind of evidence standards that are required to "approve" it for use in preclinical and clinical testing. Successful establishment of a biomarker-qualification framework would expedite and promote work by industry, academe, and government—a collaborative effort that is necessary for ultimate progress.
- *Patient-reported outcomes.* Patient focus should be a primary goal of drug development rather than merely a desirable addition. Inclusion of

patient-reported outcomes that provide insights into benefit:risk assessment is critical. Patient focus consists not merely of anecdotes but rather of a science of patient input as described further below in the section “Educating the Public, Policy Makers, and the Mass Media.” To achieve that aspiration, the emerging discipline must be developed more rapidly and deliberately.

- *Innovative clinical-trial designs.* The traditional three-phase approach (assess safety, then obtain proof of concept of efficacy and establish a dose range, and then undertake pivotal clinical trials in large populations) may not always be the optimal way to test potential medicines. Adaptive designs blur the distinctions between the phases by using predetermined enrichment schemes bolstered by advanced statistical tools, such as Bayesian statistics and modeling. For instance, a seamless or phaseless clinical-trial approach has been used in recent oncology trials. A clinical trial might be optimized to maximize speed and minimize size. Furthermore, science-based approaches to determine the appropriate representation of females vs males, underrepresented racial and ethnic groups, and so on, should be used in the recruitment of patients for trials. And pilot experiments are essential in testing new trial designs.
- *Real-world evidence.* It has been traditional practice to consider only information gained through randomized, double-blind controlled clinical trials (RCTs) in deciding the efficacy or benefit and safety of new therapies. That approach has generally served medicine well. However, the current ability to gather large amounts of data presents an opportunity to gain knowledge about the benefits and safety of drugs in a real-world setting that heretofore was not possible. Indeed, the observational biases that are inherent in the use of RWE might be mitigated on the basis of the size of a cohort and the number of observations. RWE might add important information about medicines not seen with RCTs. Early applications of RWE might be more wisely applied to supplemental applications of approved medicines to diminish safety considerations but could complement RCTs in the future. Deployment of selected pilots in a continuous learning approach to explore the value of RWE in both postapproval and preapproval settings is warranted.
- *Precision medicine.* We have used medicines in a “one-size-fits-all” paradigm too long. That is due largely to lack of knowledge about how to match a specific drug to a specific patient. The identification of groups that might benefit more from a particular drug before clinical testing has already seen applications in oncology and rare diseases in a personalized-medicine approach. In the future, a hypothesis about a population that responds to an intervention more favorably than the rest of the cohort with the disease might be posited and examined. Clinical trials could be smaller and shorter, assuming that the effect size is significantly greater in the relevant group. That would lead to improved efficiency of clinical trials and reduce exposure of subjects who probably would not benefit from a given medicine. Ideally, precise diagnosis mated with precise drugs would result in precision medicine wherein the right patient would receive the right medicine at the right dosage and at the right time.

### Clinical Trial Execution

Beyond innovative designs, there are opportunities for greater efficiency in the execution of clinical trials, as follows:

- *New technology.* Improvements are necessary to streamline the number of required procedures, site qualification, recruitment, safety monitoring, real-time data evaluation, and the informed-consent process. New technologies—such as the use of biosensors, electronic sourcing, risk-based monitoring, electronic medical record (EMR)-linked recruitment tools, and Web-enabled trials—are already being piloted and implemented, positioning the clinical-research enterprise for substantial change. The simple establishment of a single institutional review board for collaborating institutions would speed clinical trials and reduce costs. New technologies alone are insufficient to transform the operating model of clinical trials, but if they are combined with alternative trial paradigms, such as the use of remote clinical-research networks or Web-based “virtual” trials, the full cost benefit of new technologies for conducting clinical trials might be realized.
- *Decentralization of clinical trials.* Moving activities away from tertiary care centers and closer to

patients in their own communities has the potential to reduce the infrastructure costs associated with drug development dramatically. At the same time, such measures could broaden the participation of untapped groups of patients and providers who would otherwise not engage in clinical research studies.

- *Pragmatic clinical trials.* Decentralization of clinical trials and the incorporation of new digital technologies would also greatly facilitate the execution of “pragmatic clinical trials” (PCTs), which more directly address the real-world performance of new products compared with traditional RCTs. Pragmatic trials are typically designed to enroll more diverse patient populations in clinical-practice settings where compliance may be highly variable and are often integral to comparative-effectiveness research or large simple trials. Consequently, PCTs come closer than RCTs to addressing whether a product works under diverse practice conditions.
- *Integration with health care delivery.* The integration of clinical research with health care delivery presents another opportunity to transform how clinical studies are conducted, potentially gaining efficiency and reducing cost. By working with providers and information technologists to embed continuous learning, including clinical trials, in information-technology systems, such as EMRs, sponsors of clinical research could serve as a catalyst for creating what the Institute of Medicine has described as a learning health care system whereby care delivery is integrated with knowledge generation (IOM, 2007).
- *Safety assessment.* Sponsors of innovative products that hold promise for addressing unmet needs or represent important improvements over standard of care are increasingly using expedited review processes. Limited patient exposure before market entry raises the question of how to address assessment of the safety profile. Products with novel mechanisms of action can have unforeseen rare but potentially serious adverse effects that might be observed only after a large number of patients have been exposed or after a duration of exposure that exceeds what was studied in preapproval trials. That applies generally but is more acute for products coming to market via an accelerated approval pathway with a limited safety database.

Although improvements in predictive toxicology and safety assessment may mitigate the risk of adverse effects to some extent, earlier market entry of innovative products generally means that safety and effectiveness profiles are not fully elucidated. Consequently, an understanding of a potential shift in the benefit:risk ratio in the post approval setting requires continuous monitoring through such mechanisms as the FDA Sentinel initiative (FDA, 2016a), a distributed data and analytic partner network that allows queries related to medical-product safety and comparative effectiveness and education of patients, the public, and the mass media.

### Regulatory Review

Regulators increasingly will have to respond to the expectations of a wide array of stakeholders outside the biomedical-research community. The current societal imperatives—expediting products for unmet medical needs and generating better evidence to optimize therapy when alternatives exist—will probably strengthen in the next decade. Intensifying interest of patient groups, legislatures, and the mass media will lead to expansion of regulators’ tasks in such spheres as global harmonization and “regulatory convergence,” access to investigational drugs, use of real-world evidence (RWE) in regulatory decisions, clinical-trial data transparency, and response to outbreaks and pandemics. Regulators increasingly will need to take into account the needs of payers and technology assessors when considering trial design and outcome measures.

- *Regulatory convergence.* The United States has the strongest medical-product regulatory system in the world. As more and more countries try to emulate FDA, we are seeing a proliferation of global regulators and with them greater variety in regulatory standards among countries. The increasing globalization of medical-product development is leading to a stronger push toward worldwide “regulatory convergence.” For the last 2 decades, the International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH; [ich.org/home.html](http://ich.org/home.html)) has been the vehicle for development of common standards. ICH was convened primarily by the regulators and innovating pharmaceutical industries of three regions—Japan, Europe, and the United States. ICH has recently

been re-formed to recognize the global nature and broad scope of drug manufacturing and will have much broader participation by regulators and industry worldwide. Similar efforts are under way with regard to medical devices via such organizations as the International Medical Device Regulators Forum ([imdrf.org/index.asp](http://imdrf.org/index.asp)). The harmonization activities are resource intensive. Outside ICH, regulators are working together on greater harmonization of regulatory procedures. The United States is evaluating mutual reliance on manufacturing inspections with the inspectorates of countries in the European Union. FDA has the opportunity to act not only as an active participant in global regulatory convergence but as a model participant.

- *Closing the knowledge gap between innovators and regulators.* The rate of scientific progress and therapeutic innovation in all sorts of medical products is increasing exponentially. With true innovation, the innovators not only are the leading experts in a specific technology but may be the only people that fully understand all the issues at play. The knowledge gap between innovators and regulators can lead to delays in allowing pioneering therapies to reach the patients that need them the most. Initial efforts are under way by the FDA Center for Devices and Radiological Health (CDRH) to establish mechanisms to provide additional reviewer training via programs like the Experiential Learning Program (FDA, 2016b) and the Network of Experts (FDA, 2016c). However, they fall short in true technologic innovation, in which specific knowledge may not exist outside the innovators. FDA will need to explore new methods of interacting with sponsor companies and outside experts to understand the technologies that they regulate and the appropriate methods of evaluating them to ensure that US patients have timely access to all approvable therapies.
- *Access to investigational drugs.* Many states have passed “right-to-try” laws that declare a seriously ill patient’s right to request an investigational drug without government oversight. FDA approves almost all requests for patient access, but problems persist, including disparities in access to information, shortage of drug supplies, lack of access to an institutional review board, unwillingness of physicians to suggest or take responsibility for administering investigational drugs, and sponsors’ inability or unwillingness to create access programs.
- *Nonprofits are making multiple efforts to develop “patient navigator” functions to improve transparency and increase access.*
- *Postapproval evaluation of medical products.* It is clear that no matter how high the regulatory bar, premarketing studies are often imperfect in predicting real-world performance in diverse patient populations and care settings. There is great interest in using digital health care data to evaluate the performance of marketed products. The FDA Amendments Act instructed FDA to construct an active drug-safety surveillance system that would use such data. The FDA Sentinel initiative (FDA, 2016a) is operational and contains data on almost 200 million people, mainly from claims. Industry has long used RWE—data from health care settings—to describe unmet medical needs, assess the economic value of drug products, and study disease incidence, prevalence, and natural history. RWD are increasingly used by industry to conduct post-marketing comparative-effectiveness research, to characterize drug benefit:risk profiles, to facilitate postmarketing safety signal identification and evaluation, and to develop quality-of-care measures. FDA is also broadly interested in the use of RWD to generate evidence beyond drug safety. In addition to the studies described above, randomized and other types of interventional trials can be conducted in practice settings by using EMRs to capture results. FDA is exploring linkages between its Sentinel initiative and the National Patient-Centered Clinical Research Network (PCORnet; [www.pcornet.org/](http://www.pcornet.org/)), which contains EMR data, and registries and other data sources. Key priorities for the effort, which might involve FDA and possibly academia, include expanding the use and utility of common data models, establishing regulatory standards for data integrity and human-subject protection in real-world trials and data-collection efforts, improving methods for design and analysis, and building regulatory expertise in the mining, interpretation, and use of RWD to enable more timely patient access to innovative therapies.
- *Innovative regulatory policy.* The pace of therapeutic innovation is growing rapidly, often with little corresponding evolution to the dated regulatory paradigm by which the products will be judged. For example, innovation in the combination-product space (the combination of a device with a drug or

biologic) has been constrained by a regulatory system that has lacked full transparency and predictability. Recent FDA initiatives to strengthen and improve the known issues with the regulatory review of combination products are a step in the right direction, such as development of the Combination Products Policy Council (FDA, 2016d) and launching of the Lean Management Process Mapping Project (FDA, 2016e), but reveal a fundamental flaw in the current regulatory paradigm, namely, that regulatory processes are not systematically evaluated and improved unless they reach a tipping point. Ideally, medical-product stakeholders would be working in real time to assess and improve regulatory paradigms to ensure that regulatory processes are not adding unnecessary obstacles to patient access to safe and effective innovative products.

### Patient-Centered Product Development

Historically, patients have not been engaged in medical-product development beyond their participation in clinical trials. However, the paradigm is changing. Patient input from early-stage R&D through the post-approval period, including insurance-coverage decisions, is increasingly recognized as essential (Norris et al., 2015; Pogorelc, 2013). Many stakeholders—including researchers, drug developers, and FDA—are starting to engage patients to develop mutually beneficial core objectives and ensure greater public acceptance. The mandate of regulators emphasizes needs of and risks to the population, but patients have views of the benefit:risk ratio that emphasize the individual perspective. Those views often differ substantially and need to be reconciled. Engaging patients directly will ensure that medical products are designed to meet their needs and that clinical trials capture information that is relevant and specific to intended end users. Learning and change for all participants in the health ecosystem will be necessary to speed and enable the integration of patient preference into the health care system and overcome the uncertainty and unfamiliarity associated with patient-preference data.

Patient input can help greatly to identify unmet needs and set research priorities by influencing end-point selection and clinical-trial design and conduct; this will result in easier and faster clinical-trial recruitment, less burdensome trials, and the evaluation of outcomes relevant to patients (Hoos et al., 2015). By ensuring that new

products reflect patients' needs, stakeholders can avoid expensive errors. For example, billions of dollars were spent on development of Exubera, an inhalable form of insulin, but it was removed from the market after only 1 year when people who had diabetes did not see sufficient benefit from the product (Heinemann, 2008). The result of patient engagement is new treatments that meet patients' needs. The practice of including patient input throughout a product's life cycle is growing and evolving, but many challenges must be overcome to achieve a patient-centered drug-development process, including the following:

- *Incorporating patient input.* Stakeholders vary widely, so there is a clear need to identify appropriate methods, strategies, and approaches to engage with patients. Public-private partnerships could spearhead collaborative efforts to develop methodologic standards for collecting patient input and developing consensus-based guidelines. The engagement rubric released by the Patient-Centered Outcomes Research Institute (PCORI) illustrates how input from patient and stakeholder partners can be incorporated throughout the entire research continuum (PCORI, 2015). The Medical Device Innovation Consortium produced a framework for incorporating patient preferences into regulatory assessments of new medical technology, and the University of Maryland's Center of Excellence in Regulatory Science and Innovation has created a patient-focused drug-development rubric (MDIC, 2015; UMCERSI, 2015). Over the last decade, FDA has launched a number of initiatives aimed at expanding patient engagement to inform medical-product reviews. The Center for Drug Evaluation and Research (CDER) launched the Patient-Focused Drug Development program and the CDRH issued draft guidance on the use of patient-preference information in device approvals and created the Patient Engagement Advisory Committee (Enriquez, 2015; FDA, 2015, 2016f). Similar activity to engage patients is taking place globally, for example, the Patient Focused Medicine Development coalition ([patientfocusedmedicine.org](http://patientfocusedmedicine.org)) and the Innovative Medicines Initiative ([imi.europa.eu](http://imi.europa.eu)) (Hoos et al., 2015; Supple et al., 2015). Those examples demonstrate a growing acceptance of patients as partners in the development and regulatory process and urgency to target research efforts collectively.

- *Building capacity to engage with patients.* There is a need to build patient skills so that they are better prepared to engage and play a more influential role. For example, the Parkinson's Disease Foundation's learning institutes have trained nearly 300 volunteers to play a role at every level in Parkinson disease research (PDF, 2016). Similarly, the Cystic Fibrosis Foundation has worked with the medical community to establish more than 110 cystic fibrosis care centers nationwide, about 80 of which can conduct clinical trials (IOM, 2012).
- *Establishing FDA guidance.* Despite efforts to increase patient engagement in drug development, regulatory uncertainty is a major barrier to obtaining useful input (Nordrum, 2015). Industry stakeholders believe that for purposes of providing input the best patient is an informed patient. So industry researchers seek greater clarity regarding interactions with patients because of concerns that such communication might be viewed as "promotional." The patient and stakeholder communities have called on FDA to provide guidance about such topics as appropriate industry interactions with patients, incorporation of patient information on product labels, and linking of patient information to benefit:risk assessments (NHCGA, 2015). Without clear FDA guidelines that define appropriate bilateral communication between industry and patients, biopharmaceutical companies will not risk implementing innovative engagement strategies. Conversely, guidelines that are cocreated with measured input from the patient and stakeholder communities will receive greater acceptance and result in better use.
- *Defining value.* Value models have emerged recently as the latest tools for assessing the worthiness of new medical products; however, value is often confused with cost or price and described in narrow terms of cost effectiveness. Cost effectiveness may be an indicator of value from the payer perspective (and can be influenced by discounts, bundling purchases, and a one-size-fits-all population approach), but it is often unrelated to the patient perspective. For patients, value is individualized and may evolve with disease trajectory or the stage of a patient's life. In 2015, several initiatives to calculate value were released (ICER, 2016; MSKCC, 2015; NCCN, 2016; Schnipper et al., 2015),

but it is not apparent that individual patients or patient organizations were engaged in their creation or development. A collaborative effort of all stakeholders is recommended to develop an accurate value-model rubric (NHC, 2016).

Priority considerations for increasing patient engagement in developing new treatments include

- Strengthening and expanding initiatives for patient engagement, such as those under way in CDER and CDRH.
- Continuously evolving the FDA's Patient-Focused Drug Development program (FDA, 2015) to create opportunities for patients and patient organizations to provide their perspectives to FDA.
- Convening FDA and stakeholders, including the patient community, to establish methods for gathering and using patient input in drug development.
- Clarifying how FDA will evaluate and measure patient preferences and incorporate them into regulatory assessment.
- Helping to educate the patient community about drug development, regulation, and insurance coverage and about mechanisms for participating in patient-engagement efforts.
- Convening the Centers for Medicare & Medicaid Services (CMS) and stakeholders, including the patient community, to gather input for assessing the "value" of new medications and the implications for drug coverage and reimbursement.

### Speeding the Uptake of Medical Advances into Clinical Practice

Within the next decade, whole-genome sequencing and an understanding of the molecular profiles of cancers and therapies targeted to alterations in cancer have the potential to usher in an age of personalized medicine and novel approaches to drug discovery. Despite the promise of exceptional health and health care, we continue to have a disconnect between clinical knowledge and the evidence basis of care on the one hand and the care that is delivered to patients on the other hand. Clinicians, particularly primary care physicians—who are taking on a greater role as coordinators of care—and specialists, are unable to keep up with the explosion of information (over 1 million health-related publications each year). Our health

information systems do not provide sufficient clinical support and advanced analytics to guide care or innovative care models. We are living in an age of big data, but we are not optimizing the use of the data. For example, during the 1990s, many women needlessly underwent bone-marrow transplantation for breast cancer before it was shown to be an ineffective treatment.

How do we close the time gap between the development of new evidence and its integration into practice? Several notable approaches that will serve as a framework for the future are under way. They involve the use of RWE and collaborations among sectors of the health care system that will generate knowledge about the best use of drugs, devices, and clinical models of care; cognitive computing to understand the most effective and appropriate interventions for enhanced clinical outcomes; specialists working in their professional organizations to guide clinical care, reduce the current variation in care, and promote evidence-based care; harmonized quality measures and payment instruments; effective leveraging of new organizational structures and their clinical leaders; and the enabling of patients to facilitate shared information and become partners in care.

- *Distributed data networks.* One particularly important example of the more rapid translation of evidence into practice is the FDA Sentinel initiative. Working collaboratively with health care systems, health plans, and manufacturers enables FDA to monitor the safety of newly approved products by using a distributed-data model that can identify, often rapidly, safety issues and extremely rare events. The system creates a federated dataset that enables query of all participating health-plan and delivery-system data, enabling aggregation of data on more than 100 million people. PCORI, through PCORnet, and the National Institutes of Health (NIH) Collaboratory Distributed Research Network are taking similar approaches to engage key providers and advance real-world observational clinical research.
- *Cognitive computing.* Cognitive computing has been used to identify targeted treatment options for patients who have specific variants of disease. Memorial Sloan Kettering Cancer Center, for example, has been working with IBM's Watson Health ([mskcc.org/about/innovative-collaborations/watson-oncology](http://mskcc.org/about/innovative-collaborations/watson-oncology))

to enable a new paradigm for cancer care in which patient genomic data can be checked against libraries of clinical-trial data to identify treatment paradigms that are most closely tailored to a patient's particular variant of cancer. To some extent, that automates the process of matching evidence to appropriate practice-based situations in which it can be used and ensures that physicians are informed of the latest advances in science. Those approaches will find their way to consumers as people become more deeply knowledgeable about alternative approaches to care and their preferences for care.

- *Professional standard setting.* The Choosing Wisely campaign ([choosingwisely.org](http://choosingwisely.org)), developed by the American Board of Internal Medicine Foundation, exemplifies how the medical profession can best work together to synthesize evidence and drive it into practice. The campaign, aimed at determining approaches to remove waste and ineffective care from our health care system, assembled more than 70 medical-specialty organizations to identify over 300 areas of ineffective clinical care. This resulted in new guidelines about appropriate care. In connection with multiple key stakeholder organizations, including such leading consumer organizations as Consumer Reports, the new guidelines were made visible within specialties and in general public discourse. Early data suggest that the campaign has been successful in promoting the adoption of new practices and in the discontinuation of ineffective and wasteful practices.
- *Performance and quality standard setting by multiple stakeholder groups and payers.* Harmonization of performance and quality measures by health professionals, CMS and other federal agencies, and private-sector health plans can speed the implementation of new practices by creating clear expectations of practice behavior. For example, more than a decade ago, the National Committee for Quality Assurance established the prescription of beta-blockers after myocardial infarction as an important quality measure—a reflection of the best evidence on managing patients after a heart attack. That practice was eventually widely adopted to the point where nearly 100% of myocardial-infarction patients were receiving beta-blockers. The inclusion of quality measures in the Health Information Technology for Economic and Clinical Health Act

suggests that health information technology, when combined with a thoughtful approach to quality measurement, can be an important enabler of the rapid integration of evidence and new clinical standards into practice.

- *Institutional and clinical leadership.* As the structure and organization of the health care system evolves from small practices to large integrated practice structures, institutions and their clinical leaders can take an enhanced role in driving new insights into practice. Historically, clinical leaders have not had a strong role in auditing the clinical work of other physicians; physicians have been able to practice according to styles and norms of their choosing. There is a potential enhanced role for clinical leaders in integrated practice settings (large health systems, medical groups, and payer-provider entities) to drive changes into practice. Some risk is associated with it—such as potentially compromising individual clinicians' autonomy—but it has the benefit of a layer of oversight over practice patterns. Clinical leaders could provide value by coaching physicians into new practice paradigms that they might not pursue on their own.
- *The role of patients.* The historical hierarchic nature of the physician-patient relationship is changing. Physicians and patients—particularly those managing chronic illnesses—are increasingly viewed as partners. Patients have a role in speeding the use of innovations in clinical practice both by sharing the innovations with each other and by sharing them with physicians as they learn about them through their experience, the Internet, and other vehicles. The democratization of information has enabled patients to participate in such forums as Patients Like Me ([patientslikeme.com](http://patientslikeme.com)), Smart Patients ([smartpatients.com](http://smartpatients.com)), and the ImproveCareNow Network ([improvecarenow.org](http://improvecarenow.org)). The cutting-edge information that they acquire can be taken to clinicians who might not be as personally engaged in learning about a particular issue as are the patients. That powerful role reversal has the potential to drive diffusion of information from patient to physician. Physicians then may transform their practice patterns for all the patients that they serve.
- *Health care costs and affordability.* Health care costs are crowding out investment in education, housing,

and other social determinants of health and are impeding growth of wages. Using resources in the most effective ways will require new approaches to the value of health care and interventions, particularly pharmaceuticals and devices. It is vital to assess overall effects on improved health, reduction in the burden of illness, reduction in health care costs, and assessment of indirect benefits, such as increasing workplace productivity and effects on family caregivers. Such assessments in the case of hepatitis C or Alzheimer's disease will provide a far more encompassing picture than just the cost of specific therapies. Such organizations as the Institute for Clinical and Economic Review and other private-sector initiatives are stepping into the void created when federal agencies (including PCORI, the Agency for Healthcare Research and Quality, and FDA) were directed to exclude consideration of cost and value.

- *The role of medical education.* Ensuring that new medical advances are incorporated into practice in a timely fashion requires identifying the full array of stakeholders that need to be addressed. Practicing physicians are the most obvious group, but the audience is much more extensive, including non-physician practitioners (such as nurse practitioners and physician assistants), information-technology professionals who support medical practices, office-management staff, practice-based quality-improvement professionals, and payers who often set clinical standards for practice. In addition, it is critical to include future practitioners (such as medical students, residents, and subspecialty fellows) and the academic faculty who train them. Finally, patients must be informed and educated about advances—their appropriate use, value, potential harms, and potential financial obligations that they will have to bear.
- *Mechanisms for delivery of information.* Increasing time pressure on health care practitioners makes it critical that new information be transmitted concisely and that multiple vehicles be used, taking into account the diversity of ways in which health care professionals like to receive information. Although presentations of new research at scientific meetings followed by peer-reviewed journal articles are the traditional critical initial sources of information

about advances, practicing clinicians commonly do not have the time to read and absorb the original scientific data. Instead, they often depend on secondary sources in which the information is digested, interpreted, and repackaged. The secondary sources include review articles, point-of-care clinical-decision support resources, specialty society meetings and other continuing-medical-education activities, electronic journal alerts, and professional newsletters. Ultimately, clinical guidelines created by professional societies can help to shape practice patterns, but they are often less timely because of the need to accumulate a sufficient evidence basis and an inherent delay in their development and dissemination. In the future, innovative modes of data retrieval, integration, and dissemination, as exemplified by IBM's Watson Health ([ibm.com/smarterplanet/us/en/ibmwatson/health](http://ibm.com/smarterplanet/us/en/ibmwatson/health)), may become common tools.

- *Training of future physicians.* Attention needs to be paid to teaching new and existing physicians how to integrate new data into practice; indeed, the foundations of future medical practice will be much less about the specific evidence base that is in use today and much more about having the skills, values, and professionalism to continue to refresh one's approach to clinical practice. That is not a new idea, but it will be more important than ever as the evidence base grows exponentially.

### Educating the Public, Policy Makers, and the Mass Media about Clinical Data and Trials

Many of the efforts and suggestions presented in this paper will not be realized unless the knowledge and understanding of policy makers and the public are enhanced. We believe that strategic federal initiatives to increase understanding about the role of clinical trials, about the need to increase participation, and about the importance of clinical trials to society would constitute a worthwhile investment in the health of Americans.

- *Benefit:risk ratio.* The concept of "benefit:risk" is generally not well understood by patients, payers, and policy makers. Although the public and Congress expect medicines and vaccines to be "safe and effective," they often fail to understand the nature and nuance of these terms in science and

medicine. No medicine or vaccine is perfectly safe, and few are universally effective—that is, for all patients who have a given disease. We believe that a better term would be "risk:risk." Each disease increases the risk of some adverse experiences. So does each therapy. Patients and their doctors need to determine on an individual basis whether the risk of the natural progression of the disease is greater than the risks associated with a therapy. If that is not the case, they should not initiate the therapy. Government-sponsored educational programs that target the public, policy makers, and the mass media would probably carry considerable weight.

- *Product liability.* Ramifications of product liability should be addressed to balance the desire to move life-affecting therapies to market faster on the one hand with the protection of patient safety on the other. Striking the right balance is necessary to maintain appropriate incentives for continued innovation in the biopharmaceutical sector.

### Conclusions

This paper is replete with descriptions of actions now under way or recommended that would serve as levers for progress or change in policy. We conclude by reemphasizing a subset of them and highlighting options for strategic federal initiatives. New policies and strategic investment can be leveraged to create value, decrease costs, create jobs, and strengthen global leadership in health innovations by the United States. Progress is already being made to implement the strategies outlined here. Many of the new agents that are in development have the potential to transform or even cure diseases (such as some cancers or hepatitis C, respectively) for which there were no treatments in the past. The success of translational R&D is increasing, and FDA has been rising to the challenge posed by the increasing number of new drug candidates by establishing "breakthrough therapy" and other "fast-track" mechanisms to facilitate the rapid and responsible movement of important advances to patient care.

However, moving such advances to patients as rapidly as possible presents many challenges. Innovative designs for clinical trials can reduce development time and expenses. Such designs are especially effective in demonstrating "proof of concept" and determining efficacy. They can facilitate arriving at "no-go" decisions,

thus saving time and money. But there is no shortcut for assessing safety in humans. Confidence in a given “level of safety” of a drug, vaccine, or device is established by the number of people exposed, the duration of exposure, and, when appropriate, the magnitude of exposure. Shorter trials with fewer participants are inherently linked to a lower level of confidence.

Without understanding of some of the potential compromises that arise from speedier drug-development approaches, earlier regulatory approval that is based on such trials places the inventors of drugs at greater vulnerability in our litigious society, especially when society and the mass media assume that FDA approval means that a new drug is absolutely safe and effective for everyone. The legal and educational issues in this arena would benefit from strategic federal intervention.

Harmonization or convergence of regulation among countries and regions is a pressing need with respect to new medicines, vaccines, and devices. Convergence will reduce development costs, decrease patient exposure to experimental drugs and devices, and speed worthy innovations to those in need globally.

Precision medicine holds great promise. But as advances in genotyping, proteomics, and so on identify more and more populations in a given disease category, challenges to the business model for biopharmaceuticals increase. For example, although the cost of developing a precise therapy for 10% of a disease population is likely to be less than that of developing an agent generated through conventional methods, the accompanying decrease in cost is unlikely to be 90%. And although the value of such precision products is greater, the market will be much smaller than that for products prescribed without “precision” to the general population for a given disease. New approaches to determining value will be essential to provide incentives for drug invention without placing an onerous financial burden on individuals and society.

Antibiotic resistance and bioterrorism are other domains in which the business model is challenging but the needs are essential for the future health of Americans. Population medicine impels us to be good stewards of antibiotics to slow the emergence of antibiotic resistance in pathogens. However, creating antibiotics in the hope that they will be rarely, if ever, used runs counter to the conventional business model. The same

conundrum is faced in inventing vaccines and anti-infectives for agents that might be used in bioterrorism. Without government programs to address the need for innovative anti-infectives and vaccines, there is little incentive to invest over the long term, especially if other therapeutic needs do not face this challenge. Given the threat of virulent epidemics and bioterrorism, it might even be possible to address the needs through multinational programs; for example, the United States, Europe, Japan, and other countries could collaborate, dividing the labor and financial costs of programs directed at global solutions.

As discussed earlier, FDA’s Sentinel initiative is being used to detect safety signals earlier and with greater sensitivity. There is interest in using the same huge clinical database to obtain RWE of efficacy. But most clinical databases have flaws. The US government could assemble experts and stakeholders to create measures to improve the databases, set standards, and recommend appropriate methods for specific categories of inquiry.

The complexity of issues in health and medicine that our society needs to address is so enormous that no sector can devise or implement solutions on its own. The negative climate around academe–industry interactions strains current collaborations and inhibits formation of new ones. If this situation persists, the position of the United States vs global competition will be disadvantaged. NIH, FDA, other government agencies, academe, and industry could do more to reaffirm their common goals and encourage scientists, especially younger ones, to work at interfaces of these sectors.

Keeping NIH and FDA strong in leadership and funding will reap rewards in health and finances. Scientific and regulatory efforts in predictive animal models of human toxicity and efficacy and biomarkers for specific diseases, especially in neuroscience (for example, Alzheimer disease) and oncology, could speed innovation and diminish risk.

None of the means for speeding and evaluating innovation will improve health without enhancement of avenues for introducing advances into clinical care. Several mechanisms are being tried, and other promising ones are on the horizon. It is important for professionals who provide care to use them, especially in an environment of increasing (appropriate) pressure on physicians to control costs. Cost containment is

increasingly incorporated into physician-payment systems. That leads to more pressure to demonstrate the “value” of innovative therapy through comparative-effectiveness (and, when feasible, cost-effectiveness) studies. For innovations to be accepted and prescribed by physicians, their value—not only their effectiveness—must be demonstrated.

With the right policies and investment, there is good reason to believe that innovations will improve the health of Americans and people around the globe while maintaining US leadership and strengthening the US economy.

### Vital Directions

**1. Accelerate progress toward real-world evidence generation.** As clinical data move toward universal storage on digital platforms, the possibility exists to reduce the time and expense involved in the development of evidence on the effectiveness, safety, and applicability of medical interventions. Priorities include initiatives to develop data and interoperability standards, and improve data quality and accessibility, capacity to facilitate protected data sharing, and regulatory policies that allow phased introduction with evidence generation.

**2. Invest in and apply the promise of cognitive computing.** With rapidly expanding computing capability to integrate, process, and assess very large databases, opportunities develop for accelerated learning, understanding individual variation, and developing predictive modeling. Priorities include public—private initiatives targeting the science of large-dataset computing, integrating individually generated data, and communicating results.

**3. Position and equip patients and families as partner stakeholders.** To capture the advantages of the use of patient-generated data to care management and of patient involvement to care outcomes, priorities include initiatives to enable and facilitate the roles of patients and families in all clinical decision making, and to enlist their guidance and involvement in the capture, design, and use of clinical data for new knowledge.

### Summary Recommendations for Vital Directions

1. Accelerate progress toward real-world evidence generation.
2. Invest in and apply the promise of cognitive computing.
3. Position and equip patients and families as partner stakeholders.

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